Mail Stop After Final
Attorney Docket No. 25079Y

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

SENN-BILFINGER, et al. Confirmation No. 9566

Serial No. 10/826,337 Examiner: RAHMANI, N.

Filed: April 19, 2004 Group Art Unit: 1625

Title: **PRODRUGS OF IMIDAZOPYRIDINE DERIVATIVES**

Declaration under 37 CFR 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

1.0 We, Dr. Stefan Potius and Prof. Dr. Wolfgang Kromer, declare and state:

1.1 That Prof. Dr. Wolfgang Kromer is a citizen of the Federal Republic of Germany, residing at Hinterhauserstr. 5, D-78464 in Konstanz, Germany.

1.2 That Dr. Stefan Potius is a citizen of the Federal Republic of Germany, residing at Austr. 4b, D-78467 in Konstanz, Germany.

1.3 That we are joint inventors of PCT Application No. PCT/EP01/03514, International Publication No. WO 01/72756, for all designated states except CA, CO and the US, whereby the above-identified application is the United States national stage application of PCT Application No. PCT/EP01/03514.

1.4 That from 1965 to 1972, Prof. Dr. Wolfgang Kromer, studied Medicine at the Universities of Erlangen and Wüzburg, Germany.

1.5 That Prof. Dr. Wolfgang Kromer, received the degree of Doctor of Medicine in 1973 and was admitted to practice on December 10, 1973.

1.6 That Prof. Dr. Wolfgang Kromer was a Medical Assistant in Internal Medicine, Surgery and Anaesthesiology Hospital Departments from Oct. 1972 to Nov. 1973, Ward Physician in Anaesthesiology from Dec. 1973 to March 1974, and Ward Physician at the Munich University Hospital, Clinic of Neurology, from May 1974 to August 1975. Thereafter, Dr. Wolfgang Kromer was a Research Assistant at the Institute of Pharmacology at the Munich University.

1.7 That Prof. Dr. Wolfgang Kromer was licensed as a specialist in experimental pharmacology and toxicology on December 16, 1980 and as a specialist in clinical pharmacology on March 1, 1991.

1.8 That Prof. Dr. Wolfgang Kromer received a degree as a University teacher, i.e., Dr. med. habil., from Munich University on November 19, 1981, and that Dr. Wolfgang Kromer accepted a permanent position as Professor of Pharmacology at Hannover Medical School on April 15, 1982.

1.9 That Prof. Dr. Wolfgang Kromer had a sabbatical at the National Institute for Medical Research in London, UK, for six months in 1984.

1.10 That Prof. Dr. Wolfgang Kromer was appointed Head of the Department of Gastrointestinal Pharmacology at Byk Gulden Pharmaceuticals in Konstanz, Germany, on May 2, 1985, which position Dr. Wolfgang Kromer currently holds.

1.11 That Prof. Dr. Wolfgang Kromer is author of 75 original publications and scientific reviews as well as additional congress abstracts, and has lectured on pharmacology for many years at Universities including Hannover Medical School and Konstanz University.

1.12 That Dr. Stefan Postius studied Veterinary Medicine at the "Tierärztliche Hochschule Hannover" 1965-1967.

1.13 That Dr. Stefan Postius stopped these studies before start of the clinical part by the examination 'Physikum'.

1.14 That Dr. Stefan Postius switched-over to the study of biology at the "Technische Universität Hannover" and concomitantly started his thesis at the "Botanisches Institut der Tierärztlichen Hochschule Hannover" in the department of Professor Dr. G. Jacobi.

1.15 That Dr. Stefan Postius moved to Goettingen to continue the thesis at the "Institut für Biochemie der Pflanzen" with Professor Dr. G. Jacobi in 1967.

1.16 That Dr. Stefan Postius finalized his thesis with the graduation to Dr.rer.nat. at the "Georg August University" Goettingen in the academics "Plant Biochemistry, Microbiology and Organic Chemistry". Title of the thesis: "Photochemical activities of isolated chloroplasts from dark-starved plants of Spinacia oleracea" .

1.17 That Dr. Stefan Postius was employed at the "Deutsches Institut für Fernstudien" in Tübingen. Elaboration of several study letters for the "Funkkolleg Biologie" by end of 1973.

1.18 That Dr. Stefan Postius was scientific employee at the "Institut für Physiologische Chemie II" at the University of Marburg from 1974 - 1978. Contributions to the Sonderforschungsbereich "Zellenergetik and Zelldifferenzierung" investigating the influence of changes in energy metabolism with special consideration of the Pyruvate Dehydrogenase on the cell cycle distribution of Ehrlich Aszites tumor cells. Accumulation of experience in animal experiments and cell culture techniques.

1.19 That Dr. Stefan Postius had a working stay at the "B.C.P. Janssen Institut" of the University of Amsterdam in the department of Prof. Dr. J.Tager as a scholarship holder of the "Mildred Scheel Deutsche Krebshilfe e.V." Mar - Aug 1978. Contributions to the topic "Energy metabolism of isolated hepatocytes".

1.20 That Dr. Stefan Postius contributed to the set-up of the "Institut für Gerontologie" of the University of Erlangen-Nuernberg Sep 1978 – Dec 1980. Comparative investigations of the metabolic activity of isolated hepatocytes of young and old rats.

1.21 That Dr. Stefan Postius was laboratory head in the department of "Pharmakologie und Toxikologie" at "Heumann & Co GmbH" in Nuernberg from Jan 1981- Mar 1986. Contributions to the identification of histamine H2-receptor antagonists in vitro and in vivo with rats, mice, cats and dogs. Contributions to the elucidation of the cytoprotective mechanism of aluminum-containing antacids. For this piece of work the group under the leadership of Dr. med. I. Szelenyi was awarded with the "Claudius Galenus Price" in 1986.

1.22 That Dr. Stefan Postius was appointed as "Fachpharmakologe" of the german DPhG (now "Deutsche Gesellschaft für Pharmakologie und Toxikologie") in Mar 1986.

1.23 That Dr. Stefan Postius was laboratory head in the department of "Gastroenterologische Pharmakologie" at Byk Gulden, Konstanz starting with Apr 1986. Focus on the development of the intragastric pH-metry in the gastric fistula dog to identify Substituted Benzimidazoles as inhibitors of the gastric H+/K+ ATPase.

1.24 That Dr. Stefan Postius contributed to the identification of "Pantoprazole", which is approved since autumn 1994 in Germany and is now marketed world-wide. The work contributed further to the identification and characterisation of new substances, so-called reversible Proton Pump Inhibitors, APAs (Acid Pump Antagonists, APAs; now Potassium Competitive Acid Blocker, P-CABs). The pharmacologic model developped for this purpose since 1988 is still in use by now.

1.25 That Dr. Stefan Postius established the model of TNBS Colitis in the rat, an animal model for the identification of anti-IBD (Inflammatory bowel disease) compounds from 1990 – 1993.

1.26 That Dr. Stefan Postius started the work for the development of a chemical and biological data base for the collection of all relevant data from compound-sceening in 1990. This work led to the implementation of a mandatory data base by 1995 (CUBIS: Chemical and Biological Information System). Optimization of this data base was continued by him until 2001.

1.27 That Dr. Stefan Postius established different in vitro screening models for the identification of substances achieving eradication of Helicobacter in 1994. Investigations on the intracellular localization and regulation of of Helicobacter felis urease.

1.28 That Dr. Stefan Postius was appointed as "Senior Research Scientist" in 1996 at Byk Gulden, Konstanz.

1.29 That Dr. Stefan Postius extended the anti-Helicobacter screening onto L2/S2-microorganisms. Elaboration of growth-screening systems in 96er Microtiter Plate technology. Run of the first 96 MTP growth-screening at Byk Gulden. Application of these new technologies to investigate bactericidal effects against H.pylori.

1.30 That Dr. Stefan Postius contributed to the elucidation of the mechanism of action of novel anti-Helicobacter pylori substances, leading to complete eradication of H.pylori in the infected Gerbil from 1998 – 2003.

1.31 That Dr. Stefan Postius established a pneumonia model in the mouse for the identification of anti-Chlamydia pneumoniae substances from 1998 -2000. Development of a PCR in a 96 MTP format for the quantification of chlamydial DNA directly from the different tissues.

1.32 That Dr. Stefan Postius developed a pneumonia model in the mouse with Pseudomonas aeruginosa and Group B Streptococci for the investigation and characterisation of the antibacterial effect of Lung Surfactant SP-A from 1999 –2003.

1.33 That Dr. Stefan Postius developed a completely novel chronic dog model for the quantification of Transient Lower Esophageal Relaxations (TLESRs) aiming at identification of anti-GERD compounds from 2003 –2006.

1.34 That Dr. Stefan Postius is main author of 8 publications mainly dealing with gastroenterological subjects, coauthor of more than 20 publications, author of a book article, co-author of several book articles and author of numerous posters and oral presentations during scientific meetings.

1.35 That we are thoroughly familiar with evaluating chemical compounds for their antisecretory and protective action in the gastrointestinal tract of animals and humans.

1.36 That we are fully conversant with all pharmacological and structure-activity aspects of acid pump antagonists, including the chemical classes that are the subject of United States Patent Application No. 10/826,337, as well as those of the applied references WO 98/54188 to Grundler et al. and WO 98/42707 to Simon et al.

2. Traversing the rejection of claims 15-30 under 35 USC §103(a) as obvious over Grundler et al. WO 98/54188 or Simon et al. WO 98/42707 in view of Budt et. al. DE 4308095:

2.1 We have intensively studied the Official Action dated June 22, 2006 as well as the applied prior art Grundler et al. WO 98/54188, Simon et al. WO 98/42707, and Budt et. al. DE 4308095. We are aware that the examiner has rejected claims 15-30 under 35 USC §103(a) as obvious over Grundler et al. WO 98/54188 or Simon et al. WO 98/42707 in view of Budt et. al. DE 4308095.

2.2 In order to show that the compounds of the above-identified United States Patent Application No. 10/826,337 are patentably distinct from the compounds of Grundler et al. WO 98/54188 and Simon et al. WO 98/42707, comparative tests in the dog have been carried out under the supervision and guidance of Dr. Stefan Postius. The compounds identified below have been comparatively investigated in male beagle dogs upon oral administration.

2.3 The compound PC1 (soraprazan) falls within the scope of the genus of compounds described in Simon et al. WO 98/42707 and is exemplified in Example 5A of Senn-Bilfinger, US Pat. No. 6,436,953. PC1 is the compound structurally closest to the compounds described and claimed in United States Patent Application No. 10/826,337. The compound PC2 falls within the scope of the genus of compounds described in Grundler et al. WO 98/54188 and is exemplified in Senn-Bilfinger et al., US Pat. No. 6,936,623. PC2 is the compound structurally closest to the compounds described and claimed in United States Patent Application No. 10/826,337.

3.0 Comparative Testing:

3.1 Materials and Methods:

3.2 Animals:

Testing was carried out using male beagle dogs age 2 - 4 years. Each dog weighed between 12 and 19 kg.

3.3 Housing:

The animals, held in groups of 2-4 animals/group, were housed at 20-23°C, 55-65% relative air humidity under natural daylight / dark-rhythm. Usually, depending on the weather, the animals had daily outside runout in groups. Once per week, each animals body weight and general condition were assessed and noted. In addition the

fistula region of each animal was examined. The animals were used for experiments at intervals not shorter than 7 days.

3.4 Food:

The dogs received a standard dog diet "Hundeextrudat" Nr 3358 (Provimi Kliba, Kaiseraugst, Switzerland), once daily at 10 a.m. with tap water ad libitum. 20-22 hours prior to and during the day of the experiment, the animals were fasted.

3.5 Preparation of the animals and experimental equipment:

The animals had been chronically instrumented at an age of 1-2 years. A metallic (V4a or titanium) fistula was placed at the lowest part of the gastric corpus near the greater curvature. The animals recovered quickly and were trained for the study conditions not earlier than 4-6 weeks after the operation.

3.5.1 Experimental procedure:

On the experimental day, the animals were put on a frock which carries the ambulatory pH-meter with a solid state storage unit (Digitrapper pH100, Medtronic, Düsseldorf, Germany) and a programmable infusion pump (Panomat P, Disetronic, 3401 Burgdorf, Switzerland). Electric connections were led inside the frock to the gastric fistula to be connected to the combined pH-glass electrode (type 440-M3, Ingold, Medical Instruments Corp, 4500 Solothurn, Switzerland) which was inserted into the gastric metallic fistula. In order to stimulate gastric acid secretion, pentagastrin (6 µg/kg/h in an infusion volume of 0.33 µl/kg/min) was infused by pump subcutaneously, using an Abbocath-catheter placed subcutaneously and safely secured by tape on the distal part of the dog's back.

3.5.2 Experimental protocol:

After calibration of the pH electrode at pH 1 and 7 at 37°C, on day 1 registration of intragastric pH was started at 8 a.m. 1 hour later, i.e. at 9 a.m., pentagastrin infusion was started. Further 1.5 hours later, i.e. at 10:30 a.m., each animal received 9µmol/kg of the test compound orally. The experimental equipment did not affect the normal behavior of the trained dogs. About 24 hours later, i.e. at 7:30 a.m. on day 2 , when the experimental run was completed, the pH measuring system was recalibrated in order to detect potential drifts in electrode sensitivity. A drift of less than 0.2 pH units during a 24 hour period was tolerated. Electrodes displaying a larger drift or

occasional, unexplainable pH changes during the 24 hours were discarded and the experiments were repeated. These precautions proved to be necessary because this type of electrode assembly is extremely sensitive to mechanical distortion which may occur during a 24 hour run in freely moving animals.

3.5.3 Gastric functional state:

Acid secretion was maximally stimulated by continuous subcutaneous infusion of pentagastrin from 09:00 a.m. to 07:30 a.m. on day 2.

3.6 Controls:

For each animal, a drug-free control run was done. On the control runs, animals received a saline-filled hard gelatin capsule at the time of drug administration, i.e. at 10:30 a.m.

3.7 Evaluation of pH-data:

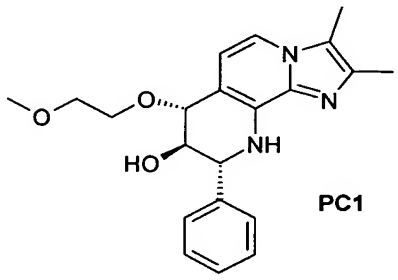
At the end of each run, pH readings (86400 readings within 24 hours, each covering 1 second) were transferred to a PC by special software (Polygram98, Medtronics, 40547 Düsseldorf, Germany), yielding individual 24 hour pH-profiles. Applying a second program (StatpHac2000, the novel, Windows2000- and Polygram98- compatible version programmed by Leif Fransson, Karlskrona, Schweden), the individual pH-profiles of one treatment group were processed to establish pH-medians for intervals of 10 minutes each, covering a total of 24 hours (144 x 10 min).

3.8 Statistics:

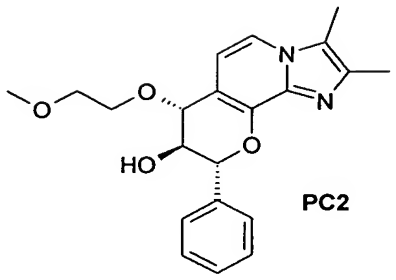
Statistical comparisons between treatment and control groups with respect to the significance of intragastric pH-elevating effects were performed on the basis of AUC values, calculated by use of the program "StatpHac2000" (Leif Fransson, Karlskrona, Sweden) for the time periods of the individual pH-profiles, where an effect of the substance was apparent. After correction of these AUC-values by subtraction of the respective control values, they were evaluated by means of student t-test using "Origin" (Vers. 7.0).

4.0 Chemical Structures of tested compounds:

4.1 Structurally closest related compounds:

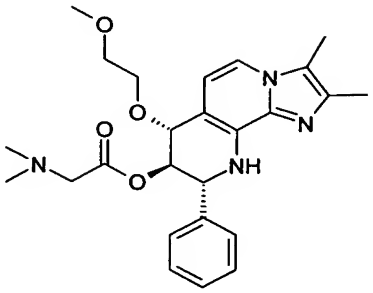


PC1

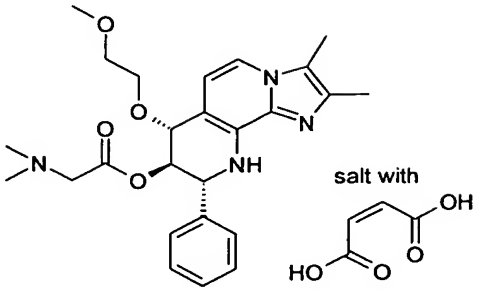


PC2

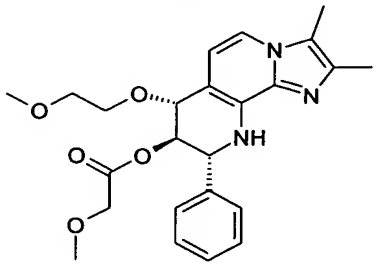
4.2 Compounds according to the presently pending claims:



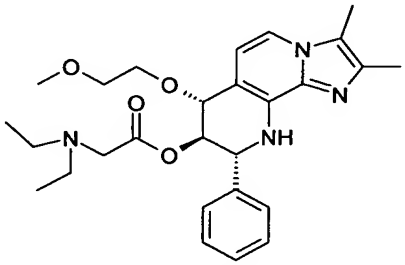
20



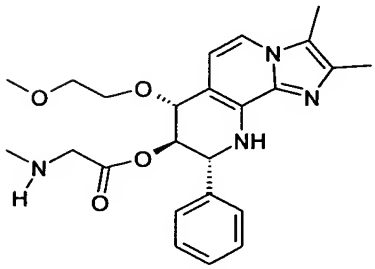
48*



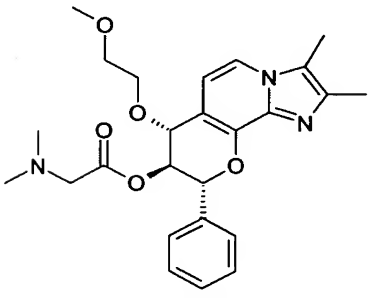
49*



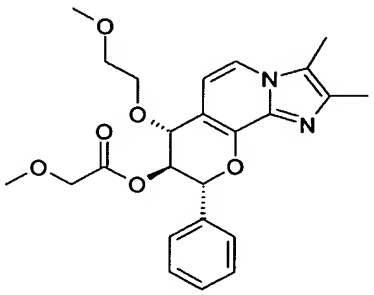
50*



51*



52*



53*

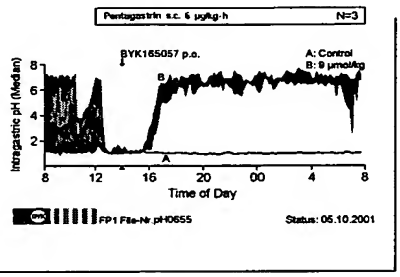
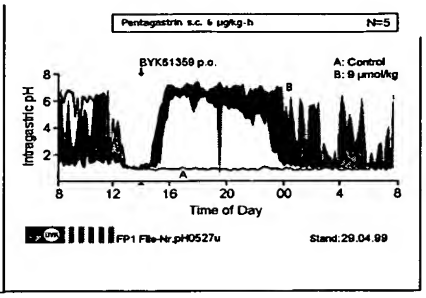
* Compounds 48-53 fall within the scope of present claim 1. However, they are not expressly described in the present application.

5.0 Results:

5.1 24-hour pH-profiles:

Typical 24h pH-profiles obtained according to the procedure described above are shown in the following Table 1, where the presently claimed compound (example 20) is compared to compound PC1:

5.2 Table 1:

Present compound Example No. 20:		PC1:	

5.3 Antisecretory Activity:

In the following Table 2, the impact of the present claimed compounds 20 and 48-53 on antisecretory activity in the pentagastrin stimulated fistula dog (intragastric 24 h pH-metry) is shown by way of comparison of the AUC values observed upon administration the present compounds with the AUC levels observed upon administration of PC1 or PC2.

5.4 Table 2:

Structurally closest compound	AUC - control	Present compound Example No.	AUC - control	**Gain by present compound Principle AUC)**	**Gain in % (structurally closest compound = 100%)**
PC1	50250	20	75450	**25200**	**50**
PC1	50250	48	84000	**33750**	**67**
PC1	50250	49	82950	**32700**	**65**
PC1	50250	50	74700	**24450**	**49**
PC1	50250	51	61200	**10950**	**22**
PC2	48300	52	60000	**11700**	**24**
PC2	48300	53	81750	**33450**	**69**

6.0 Comparative Testing Conclusion:

The introduction of a presently claimed residue, exemplified by the type –C(O)-R8 with R8 = 1-4C-alkyl substituted by 1-4C-alkoxy or by the type –C(O)-alk-NR8R9, in the R5 position as present in the compounds 20 and 48 – 53 results upon administration of the present compounds in an increase of AUC levels of more than 20% as compared to the AUC levels observed upon administration of PC1 or PC2 which are substituted with only a hydroxyl group in the R5 position.

6.1 This data evidences the unexpectedly superior results achieved by compounds 20 and 48 – 53 according to the presently pending claims as compared to the structurally closest compounds PC1 and PC2. The data clearly illustrates that compounds 20 and 48-53 according to the presently pending claims exhibit unexpectedly superior efficacy as compared to the efficacy of the structurally closest compounds PC1 and PC2.

6.2 In view of the data shown under item 5.4, neither the Simon et al. reference nor the Grundler et al. reference in view of Budt et. al. DE 4308095, render claims 15-30 of United States Patent Application No. 10/826,337 obvious.

7.0 Further Testing:

In order to show the antisecretory potency of compounds 1-6, 8-12, 15-17, 19-20, 28, 30, 32,34, 36, 38-39,43-45 and 47 described at pages 27-37 of the specification of United States Patent Application No. 10/826,337, these compounds were tested for antisecretory activity in rat stomach primarily under the supervision and guidance of Prof. Dr. Wolfgang Kromer as outlined below.

8.0 Further Test Results:

The pharmacological testing of compounds 1-6, 8-12, 15-17, 19-20, 28, 30, 32,34, 36, 38-39,43-45 and 47 was performed in the same animal model as previously described in United States Patent Application No. 10/826,337 as filed. However, the compounds were administered intraduodenally in a 2.5 ml/kg liquid volume 60 min. after the start of the continuous pentagastrin infusion. The following Table 3 shows the influence of the present compounds on the pentagastrin stimulated acid secretion of the perfused rat stomach *in vivo* after intraduodenal administration.

8.1 Table 3:

No.	Dose (µmol/kg) i.d.	Inhibition of acid secretion (%)
1	1	> 50
2 *	1	> 50
3 *	1	> 50
4 *	1	> 50
5 *	1	> 50
6 *	1	> 50
8 *	1	> 50
9	1	> 50
10 *	1	> 50
11 *	1	> 50
12 *	1	> 50
15 *	1	> 50
16	1	> 50
17 *	1	> 50
19 *	1	> 50
20 *	1	> 50
28 *	1	> 50
30 *	1	> 50
32 *	1	> 50
34 *	1	> 50
36 **	1	> 50
38 *	1	> 50
39	1	> 50
43 *	1	> 50
44 *	1	> 50
45 *	1	> 50
47 *	1	> 50

*) Compound tested up to 0.3 µmol/kg which dose already caused an inhibition of > 50 %, and therefore > 50% inhibition at the higher dose of 1 µmol/kg has been concluded by extrapolation.
**) Compound 36 showed 45 % inhibition at 0.3 but 100 % inhibition at 0.6 µmol/kg.

9.0 Further Testing Conclusion:

The test results exemplified in Table 3 above clearly establishes that each of the presently claimed compounds 1-6, 8-12, 15-17, 19-20, 28, 30, 32, 34, 36, 38, 39, 43-45, and 47, described on pages 27-37 of the specification, inhibits acid secretion *in vivo* by more than 50 %. This data evidences a high antisecretory potency of the presently claimed compounds substituted with a wide chemical range of residues resulting in different chemical structures.

10.0 The undersigned Declarants each declare further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statement may jeopardize the validity of the application or any patent issuing thereon.

Signed at Konstanz,
Federal Republic of Germany,

Sep. 28, 2006
Date

Dr. Stefan POSTIUS

Aug. 28, 2006
Date

Prof. Dr. Wolfgang KROMER